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(54) **Oral composition containing carrier-bound antimicrobials.**

(57) There is disclosed an oral composition including an organosilicon-type quaternary ammonium salt immobilized on a water-insoluble solid carrier. In particular, an oral composition in an aqueous system according to the present invention includes an organosilicon-type quaternary ammonium salt immobilized on a water-insoluble solid carrier in combination with at least one surfactant selected from the group consisting of polyoxyethylene-polyoxypropylene block copolymers and alkylolamides as a stabilizing agent; at least one thickening agent selected from the group consisting, of nonionic thickening agents and cationic thickening agents; and optionally at least one alcohol selected from the group consisting of ethanol, propanol and isopropanol as a dispersing agent.

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The present invention relates to a composition for oral cavities. More particularly, it relates to an oral composition having bactericidal activity to eliminate microorganisms in oral cavities, thereby exhibiting a plaque-controlling effect.

It is well known that organosilicon-type quaternary ammonium salts immobilized on water-insoluble solid carriers (hereinafter referred to as organosilicon-type immobilized bactericides) have antibacterial activity. The bactericides of this type have been used as antibacterial agents for fiber treatment, as water treatment agents or as antibacterial agents to be incorporated into plastics (see, e.g., JP-A 177284/1987, JP-A 196810/1991 and JP-B 019860/1977). The application of organosilicon-type immobilized bactericides has not yet, however, been proposed in the field of oral hygiene.

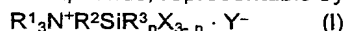
In the field of oral hygiene, it is well known that conventional water-soluble quaternary ammonium compounds such as cetylpyridinium chloride or benzethonium chloride can be stably blended into dentifrice (see, e.g., JP-A 85310/1986 and USP No. 5,035,880). There is, however, no disclosure of water-insoluble immobilized bactericides in any literature of this field.

In general, organosilicon-type immobilized bactericides have a cationic character to react with any anionic ingredient, such as a foaming agent or a thickening agent, which is usually used in conventional oral compositions, thereby causing a significant decrease in their antibacterial activity. Further, organosilicon-type immobilized bactericides in particulate form have a tendency to aggregate in an aqueous system, so that it is difficult to disperse the particles and attain uniform blending of the bactericides into an aqueous oral composition. Therefore, when an organosilicon-type immobilized bactericide is used in an aqueous system, it is necessary to devise some means for stabilization of this bactericide.

Surprisingly, the present inventors have found that water-insoluble immobilized bactericides of the organosilicon type can be satisfactorily utilized for oral compositions. They have also found that the effects of organosilicon-type immobilized bactericides in an aqueous system can be remarkably improved by blending with a particular stabilizing agent and a particular thickening agent, and these effects can be further improved by addition of a particular alcohol, thereby completing the present invention.

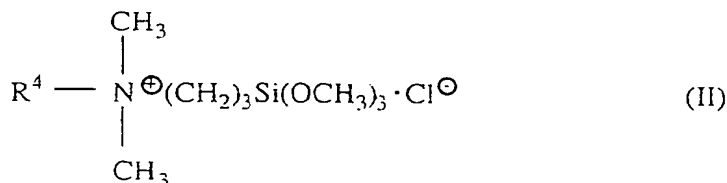
Thus, the present invention provides an oral composition comprising an organosilicon-type quaternary ammonium salt immobilized on a water-insoluble solid carrier. Preferably, an oral composition in an aqueous system according to the present invention comprises an organosilicon-type quaternary ammonium salt immobilized on a water-insoluble solid carrier in combination with at least one surfactant selected from the group consisting of polyoxyethylene-polyoxypropylene block copolymers and alkylolamides as a stabilizing agent; at least one thickening agent selected from the group consisting of nonionic thickening agents and cationic thickening agents; and optionally at least one alcohol selected from the group consisting of ethanol, propanol and isopropanol as a dispersing agent. In our work, we found that we can make compositions which exhibit excellent plaque-controlling effect not only by attaining effective bactericidal action and elimination of microorganisms in oral cavities but also by preventing accumulation and calcification of their products.

The oral composition of the present invention contains an organosilicon-type quaternary ammonium salt as a bactericide, which is immobilized on a water-insoluble solid carrier. Organosilicon-type quaternary ammonium salts are a well-known class of compounds, representable by the formula:



wherein X is a hydrolyzable group such as halogen, alkoxy or acyl; Y is chlorine or bromine; R¹'s are independently monovalent aliphatic hydrocarbon groups having 1 to 22 carbon atoms, with particularly preferred being the case where two of three R¹'s are both methyl and the other R¹ is alkyl having 8 to 22 carbon atoms; R² is a divalent hydrocarbon group, with particularly preferred R² being alkylene having 2 to 4 carbon atoms or a group of the formula: -CH₂CH₂CH₂NHCH₂CH₂-; R³ is lower alkyl such as methyl, phenyl or a group of the formula: CF₃CH₂CH₂-; n is an integer of 0 which is preferred, 1 or 2. This compound is usually available as an alcoholic solution from various commercial sources.

Preferred are the organosilicon-type quaternary ammonium salts of the general formula:



wherein R⁴ is alkyl having 8 to 22 carbon atoms.

ing 8 to 18 carbon atoms, such as sodium lauryl sulfate and sodium myristyl sulfate, α -olefin sulfonate, higher fatty acid sodium monoglyceride monosulfate, sodium N-methyl-N-palmitoyl tauride, sodium N-lauroyl- β -alanine, lauroyl sarcosinate and sodium N-long chain acyl basic amino acids.

These surfactants can be used alone or in combination. The amount of surfactant to be used is usually in the range of 0.01% to 20% by weight, preferably 0.05% to 10% by weight, based on the total weight of the composition.

Examples of the thickening agent are cellulose derivatives such as sodium carboxymethyl cellulose; alginates of alkali metals, such as sodium alginate; propylene glycol alginate esters; gums such as xanthan gum, tragacanth gum, karaya gum, arabic gum and carrageenan; synthetic thickening agents such as polyvinyl alcohol, sodium polyacrylate, carboxyvinyl polymers and polyvinyl pyrrolidone; and inorganic thickening agents such as silica gel, aluminum silica gel, bee gum and Laponite. These thickening agents can be used alone or in combination. The amount of thickening agent to be used is usually in the range of 0.3% to 5% by weight, based on the total weight of the composition.

Examples of the viscosity builder are sorbit, glycerin, ethylene glycol, propylene glycol, 1,3-butylene glycol, polyethylene glycol, polypropylene glycol, xylitol, maltitol and lactitol. These viscosity builders may be used alone or in combination. The amount of viscosity builder to be used is usually in the range of 5% to 70% by weight, based on the total weight of the composition.

Examples of the flavoring agent are menthol carboxylic acid, anethole, eugenol, methyl salicylate, limonene, cymene, n-decyl alcohol, citronellol, α -terpineol, methyl acetate, citronellyl acetate, methyl eugenol, cineole, linalool, ethyl linalool, vanillin, thymol, spearmint oil, peppermint oil, lemon oil, orange oil, sage oil, rosemary oil, cinnamon oil, pellira oil, gaultheria oil, clove oil and eucalyptus oil. These flavoring agents may be used alone or in combination. The amount of flavoring agent to be used is usually in the range of about 0.1% to 10% by weight, preferably about 0.5% to 5% by weight, based on the total weight of the composition.

Examples of the sweetener are saccharin sodium, Acesulfame K, stevioside, neo-hesperidyl dihydrochalcone, glycyrrhizin, perillartine, thaumatin, aspartylphenylalanine methyl ester and p-methoxycinnamic aldehyde. These sweeteners may be used alone or in combination. The amount of sweetener to be used is usually in the range of 0.01% to 1% by weight, preferably 0.05% to 0.5% by weight, based on the total weight of the composition.

Examples of the therapeutic agent are cationic bactericides such as cetylpyridium chloride and chlorhexidine salts; nonionic bactericides such as tricosan; amphoteric bactericides such as dodecylaminoethylglycine; enzymes such as dextranase, amylase, protease, mutanase, lysozyme and lytic enzymes; monofluorophosphates of alkali metals, such as sodium monofluorophosphate and potassium monofluorophosphate; fluorides such as sodium fluoride and stannous fluoride; tranexamic acid and ϵ -amino-capric acid; aluminum chlorhydroxyl allantoin; dihydrocholesterol, glycyrrhizin salts, glycyrrhetic acid, glycerophosphate, chlorophyll, sodium chloride, caropeptide and water-soluble compounds of inorganic phosphoric acid. These therapeutic agents may be used alone or in combination.

The present invention will be further illustrated by way of the following experiments, examples and comparative examples. Unless otherwise indicated, percents (%) are all by weight.

Experiments

Various organosilicon-type immobilized bactericides were prepared by immobilizing organosilicon-type quaternary ammonium salts of the general formula (II) on water-insoluble solid carriers as shown in Table 1, and these bactericides were evaluated for their bactericidal activities and microorganism elimination effects according to the following procedures. The results are shown in Table 1.

Procedures for evaluation of microorganism elimination effects

(1) Preparation of test bacterial suspension

The cultures of *Streptococcus sobrinus* OMZ176 were incubated in a brain-heart-infusion liquid medium under anaerobic conditions at 37°C for 20 hours, and then harvested by centrifugation at 7000 rpm for 10 minutes. The bacterial cells thus obtained were washed with sterilized physiological saline and suspended in sterilized physiological saline to yield a bacterial concentration of about 10^7 cells/ml ($OD_{560}=0.02$), resulting in a test bacterial suspension.

(2) Evaluation of microorganism elimination ratio (shake flask method)

A prescribed amount of the sample was put in a 100-ml Erlenmeyer flask, to which 36 ml of sterilized water was then added to achieve sufficient dispersion of the sample. The Erlenmeyer flask was placed in a thermostat at 37°C, to which 4 ml of the test bacterial suspension prepared in (1) was added, and the resulting mixture was shaken at 120 strokes/min. for 3 minutes.

The Erlenmeyer flask was removed from the thermostat and allowed to stand for some time, after which

1 ml of the supernatant was taken and diluted with sterilized physiological saline. Then, 0.1 ml of this dilution was smeared on a brain-heart-infusion agar plate, and this plate was incubated under anaerobic conditions at 37°C for 48 hours, followed by counting of the colony number. The viable cell number after contact with the sample for 3 minutes can be calculated from the colony number.

The microorganism elimination ratio (%) of the sample was evaluated by the following equation, and it was determined that the sample had excellent microorganism elimination effects when exhibited a microorganism elimination ratio of 90% or more.

$$\text{Microorganism elimination ratio (\%)} = \frac{\left(\text{Initial viable cell number} \right) - \left(\text{Viable cell number after contact after 3 minutes} \right)}{\left(\text{Initial viable cell number} \right)} \times 100$$

TABLE 1

No.	Sample		Concentration (%)	Microorganism elimination ratio (%)
	Solid carrier	C _n ^{*)}		
1	Cellulose powder	C ₁₈	1.0	97
2	Silica	C ₁₈	1.0	96
3	Calcium hydrogen-phosphate	C ₁₈	1.0	97
4	Zeolite	C ₁₈	1.0	98
5	Zeolite	C ₁₈	0.0005	70
6	Zeolite	C ₁₈	50	99
7	Zeolite	C ₆	1.0	35
8	Cellulose powder	—	1.0	3
9	Silica	—	1.0	6
10	Calcium hydrogen-carbonate	—	1.0	5
11	Zeolite	—	1.0	8
12	Control (water)	—	—	0

*) The symbol "C_n" denotes the length of alkyl chain (R⁴) in the organosilicon-type quaternary ammonium salts of the general formula (II); and the symbol "—" indicates no use of these quaternary ammonium salts immobilized on the solid carriers.

As can be seen from Table 1, the samples 1-7, particularly the samples 1-4 and 6, exhibited apparently higher microorganism elimination ratio, as compared with the samples 8-11 containing only the solid carrier on which the organosilicon-type quaternary ammonium salt was not immobilized. It was also found that the microorganism elimination effects of the samples 4-6 depend on the concentration of immobilized bactericides and the extremely high elimination ratio was obtained at a concentration of 0.001% to 50%. Further, stronger microorganism elimination effects were achieved in the case of longer alkyl chain length (C_{18}) than the case of shorter alkyl chain length (C_6) for the organosilicon-type quaternary ammonium salts.

Then, it was examined whether the addition of a particular alcohol as the dispersing agent had an influence on the microorganism elimination effects.

The sample 2 (shown in Table 1) as an organosilicon-type immobilized bactericide was mixed with any one of the alcohols (10 wt%) as shown in Table 2 below. The dispersing state of the resulting mixture was determined by visual observation and the microorganism elimination ratio was evaluated according to the procedures as described above. The results are shown in Table 2.

TABLE 2

Dispersing agent	Dispersing state (by visual obs.)	Elimination ratio (%)
Ethanol	good	99
Isopropanol	good	99
1,3-butylene glycol	good	80
Propylene glycol	good	80
Glycerin	good	80
No addition	poor	80

As can be seen from Table 2, the mixtures prepared with the addition of ethanol or isopropanol exhibited extremely higher microorganism elimination effects as compared with those prepared with the addition of any other alcohol or no addition.

Next, it was examined whether the concentration of alcohol to be added had an influence on the improvement of the microorganism elimination effects.

The sample 2 (shown in Table 1) as an organosilicon-type immobilized bactericide was mixed with either ethanol or isopropanol at any one of the amounts as shown in Table 3 below. The microorganism elimination ratio was evaluated according to the procedures as described above. The results are shown in Table 3.

TABLE 3

Dispersing agent	Amount (wt%)	Elimination ratio (%)
No addition	-	80
Ethanol	0.01	94
	1	99
	10	99
	30	99
Isopropanol	0.01	93
	1	98
	10	99
	30	99

As can be seen from Table 3, the mixtures prepared with the addition of ethanol or isopropanol at an amount of 0.01 wt% or more exhibited an improvement of the microorganism elimination effects as compared

with that prepared with no addition of alcohols.

Example 1

An organosilicon-type quaternary ammonium salt of the general formula (II) wherein the alkyl chain R⁴ has 18 carbon atoms was immobilized on the surface of silica powder particles to form an organosilicon-type immobilized bactericide. The organosilicon-type immobilized bactericide (1.0 wt%) was blended with PLURONIC F-88 (average polymerization degree: ethylene oxide, 194; and propylene oxide, 39; 2.0 wt%) as the stabilizing agent, hydroxyethyl cellulose (2.0 wt%) as the thickening agent, calcium hydrogenphosphate (30 wt%), glycerin (20 wt%), flavor (1 wt%), saccharin sodium (0.2 wt%) and water (the balance). The mixture was well stirred to give a dentifrice composition according to the conventional procedures. The resulting dentifrice composition was evaluated for microorganism elimination effects according to the procedures as described above. The microorganism elimination ratio of this composition was 92%.

The dentifrice composition of this example exhibited extremely strong microorganism elimination effects and stable characteristics with no occurrence of solid-liquid separation, because a polyoxyethylene-polyoxypropylene block copolymer and a nonionic thickening agent were used.

Example 2

A dentifrice composition was prepared in the same manner as described in Example 1, except that cationically-modified hydroxyethyl cellulose (2.0 wt%) was used in place of hydroxyethyl cellulose as the thickening agent. The resulting dentifrice composition was evaluated for microorganism elimination effects according to the procedures as described above. The microorganism elimination ratio of this composition was 90%.

The dentifrice composition of this example exhibited extremely strong microorganism elimination effects and stable characteristics with no occurrence of solid-liquid separation, because a polyoxyethylene-polyoxypropylene block copolymer and a cationic thickening agent were used.

Example 3

A dentifrice composition was prepared in the same manner as described in Example 1, except that PLURONIC F-127 (average polymerization degree: ethylene oxide, 196; and propylene oxide, 67; 2.0 wt%) was used in place of PLURONIC F-88 (average polymerization degree: ethylene oxide, 194; and propylene oxide, 39) as the stabilizing agent. The resulting dentifrice composition was evaluated for microorganism elimination effects according to the procedures as described above. The microorganism elimination ratio of this composition was 90%.

The dentifrice composition of this example exhibited extremely strong microorganism elimination effects and stable characteristics with no occurrence of solid-liquid separation, because a polyoxyethylene-polyoxypropylene block copolymer and a nonionic thickening agent were used.

Example 4

A dentifrice composition was prepared in the same manner as described in Example 1, except that lauric acid diethanolamide (2.0 wt%) was used in place of PLURONIC F-88 as the stabilizing agent. The resulting dentifrice composition was evaluated for microorganism elimination effects according to the procedures as described above. The microorganism elimination ratio of this composition was 92%.

The dentifrice composition of this example exhibited extremely strong microorganism elimination effects and stable characteristics with no occurrence of solid-liquid separation, because an alkylolamide and a non-ionic thickening agent were used.

Example 5

A dentifrice composition was prepared in the same manner as described in Example 1, except that coconut oil fatty acid diethanolamide (2.0 wt%) was used in place of PLURONIC F-88 as the stabilizing agent. The resulting dentifrice composition was evaluated for microorganism elimination effects according to the procedures as described above. The microorganism elimination ratio of this composition was 90%.

The dentifrice composition of this example exhibited extremely strong microorganism elimination effects and stable characteristics with no occurrence of solid-liquid separation, because an alkylolamide and a non-ionic thickening agent were used.

Comparative Example 1

5 A dentifrice composition was prepared in the same manner as described in Example 1, except that polyoxyethylene sorbitan monolaurate (2.0 wt%) was used in place of PLURONIC F-88 as the stabilizing agent. The resulting dentifrice composition was evaluated for microorganism elimination effects according to the procedures as described above. The microorganism elimination ratio of this composition was 34%.

10 The dentifrice composition of this example did not exhibit satisfactory microorganism elimination effects, because a nonionic surfactant other than polyoxyethylene-polyoxypropylene block copolymers and alkylolamides was used as the stabilizing agent, although a nonionic hydroxypropyl methyl cellulose was used as the thickening agent, whereby the organosilicon-type immobilized bactericide was not stabilized.

Comparative Example 2

15 A dentifrice composition was prepared in the same manner as described in Example 1, except that polyoxyethylene hardened castor oil (60 E.O.; 2.0 wt%) was used in place of PLURONIC F-88 as the stabilizing agent. The resulting dentifrice composition was evaluated for microorganism elimination effects according to the procedures as described above. The microorganism elimination ratio of this composition was 33%.

20 The dentifrice composition of this example did not exhibit satisfactory microorganism elimination effects, because a nonionic surfactant other than polyoxyethylene-polyoxypropylene block copolymers and alkylolamides was used as the stabilizing agent, although a nonionic hydroxypropyl methyl cellulose was used as the thickening agent, whereby the organosilicon-type immobilized bactericide was not stabilized.

Comparative Example 3

25 A dentifrice composition was prepared in the same manner as described in Example 1, except that the organosilicon-type immobilized bactericide was not used. The resulting dentifrice composition was evaluated for microorganism elimination effects according to the procedures as described above. The microorganism elimination ratio of this composition was 5%.

30 The dentifrice composition of this comparative example did not exhibit microorganism elimination effects, because the organosilicon-type immobilized bactericide was not blended therein, although the same stabilizing agent and the same thickening agent as those used in Example 1 were used.

Example 6

35 A dentifrice composition was prepared from the following formulation according to the conventional procedures.

Ingredients	Amounts (wt%)
Sample 4 (shown in Table 1)	0.5
Cethylpyridium chloride	0.1
Sodium monofluorophosphate	0.7
PLURONIC F-88	2.0
(average polymerization degree: ethylene oxide, 194; and propylene oxide, 39)	
Cationically-modified hydroxyethyl cellulose	2.0
Aluminum hydroxide	20.0
Glycerin	20.0
Flavor	1.0
Saccharin sodium	0.2
Purified water	Balance

The dentifrice composition obtained was evaluated for the microorganism elimination ratio according to the procedures as described above, and it exhibited good microorganism elimination effects and excellent feeling of use.

Example 7

A cream composition for gingival massage was prepared from the following formulation according to the conventional procedures.

Ingredients	Amounts (wt%)
Sample 1 (shown in Table 1)	5.0
Tocopherol nicotinate	0.5
PLURONIC F-77	2.0
(average polymerization degree: ethylene oxide, 104; and propylene oxide, 35)	
Hydrophobically-modified hydroxyethyl cellulose	3.0
[carbon number of hydrophobic groups, 18]	
Glycerin	20.0
Ethanol	3.0
Flavor	0.6
Dipotassium glycyrrhizinate	0.1
Purified water	Balance

The cream composition for gingival massage obtained was evaluated for the microorganism elimination ratio according to the procedures as described above, and it exhibited good microorganism elimination effects and excellent feeling of use.

Example 8

A toothpowder composition was prepared was prepared from the following formulation according to the conventional procedures.

Ingredients	Amounts (wt%)
Sample 4 (shown in Table 1)	2.0
Calcium hydrogenphosphate	50.0
Calcium carbonate	20.0
Lauric acid diethanolamide	1.0
Glycerin	20.0
Flavor	1.0
Saccharin sodium	0.1
Purified water	Balance

The toothpowder composition obtained was evaluated for the microorganism elimination ratio according to the procedures as described above, and it exhibited good microorganism elimination effects and excellent feeling of use.

Example 9

A toothwash composition was prepared from the following formulation according to the conventional procedures.

Ingredients	Amounts (wt%)
Sample 2 (shown in Table 1)	0.5
Cationically-modified cellulose	2.0
Coconut oil fatty acid diethanolamide	1.0
Sorbit	30.0
Saccharin sodium	0.1
Flavor	1.0
Chlorthexizine gluconate	0.5
Ethanol	10.0
Isopropanol	5.0
Methyl paraoxybenzoate	0.1
Water	Balance

The toothwash composition obtained was evaluated for the microorganism elimination ratio according to the procedures as described above, and it exhibited good microorganism elimination effects and excellent feeling of use.

Example 10

A mouth wash composition was prepared from the following formulation according to the conventional procedures.

Ingredients	Amounts (wt%)
Sample 1 (shown in Table 1)	0.5
Glycerin	10.0
Ethanol	15.0
Saccharin sodium	0.1
Flavor	0.3
PLURONIC F-127	1.0
(average polymerization degree: ethylene oxide, 196; and propylene oxide, 67)	
Cationically-modified guar gum	0.2
Paraoxybenzoate ester	0.1
Water	Balance

The mouth wash composition obtained was evaluated for the microorganism elimination ratio according to the procedures as described above, and it exhibited good microorganism elimination effects and excellent feeling of use.

Example 11

A chewing gum composition was prepared from the following formulation according to the conventional procedures.

<u>Ingredients</u>	<u>Amounts (g)</u>
Gum base*)	20
Sugar	58
Glucose	10
Corn syrup	10
Hydroxyethyl cellulose	1
Flavor	1
	<hr/>
	100 g

*) Gum base was prepared from the following formulation.

Ingredients	Amounts (g)
Sample 2 (as shown in Table 1)	20
Natural chicle	15
Vinyl acetate resin	25
Ester gum	10
Wax	15
Lauric acid diethanolamide	5
Isopropanol	10
	100 g

The chewing gum composition obtained was evaluated for the microorganism elimination ratio according to the procedures as described above, and it exhibited good microorganism elimination effects and excellent feeling of use.

Example 12

A dental floss composition was prepared by immobilizing an organosilicon quaternary ammonium salt of the general formula (II) wherein the alkyl chain R^4 has 18 carbon atoms on the surface of nylon floss as the water-insoluble solid carrier.

The dental floss composition obtained was evaluated for the microorganism elimination ratio according to the procedures as described above, and it exhibited good microorganism elimination effects.

Claims

1. An oral composition comprising an organosilicon-type quaternary ammonium salt immobilized on a water-insoluble solid carrier.
2. An oral composition according to claim 1, wherein the organosilicon-type quaternary ammonium salt is trialkoxysilylalkyltrialkylammonium halide.
3. An oral composition according to claim 1 or claim 2 wherein the water-insoluble solid carrier is selected from siliceous materials and cellulosic materials.
4. An oral composition according to any one of the preceding claims comprising at least one surfactant selected from polyoxyethylene-polyoxypropylene block copolymers and alkylolamides.
5. An oral composition according to any one of the preceding claims comprising at least one thickening agent selected from nonionic thickening agents and cationic thickening agents.
6. An oral composition according to claim 5, wherein the nonionic thickening agent is hydroxyethyl cellulose, hydroxypropylmethyl cellulose, hydrophobically-modified hydroxyethyl cellulose or hydrophobically-modified hydroxypropylmethyl cellulose.
7. An oral composition according to claim 5, wherein the cationic thickening agent is cationically-modified hydroxyethyl cellulose.
8. An oral composition according to any one of the preceding claims, further comprising at least one alcohol selected from ethanol, propanol and isopropanol.
9. A method comprising the preparation of a component according to any one of claims 1 to 8, by mixing the ingredients thereof.



European Patent
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EUROPEAN SEARCH REPORT

Application Number

EP 93 30 4628

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
Y	WO-A-7 900 454 (MINNESOTA MINING AND MANUFACTURING COMPANY) * page 4, line 10 - page 6, line 3; claims 1-10 *	1-3,5-6, 8-9	A61K7/16 A61K31/695 A61K47/48
Y	EP-A-0 101 027 (H. RUPPRECHT) * page 11, line 1 - line 20; claims 1-4 *	1-3,5-6, 8-9	
A	FR-A-2 342 740 (PHARMACO INC.) * page 10, line 29 - line 40; claims 1-11 *	1	
A	US-A-4 615 882 (R. F. STOCKEL) * abstract *	1	
A	US-A-5 013 459 (R. L. GETTINGS ET AL.) * abstract *	1	
D	& JP-A-3 196 810 (...)		
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			A61K C07F
The present search report has been drawn up for all claims			
Place of search BERLIN		Date of completion of the search 20 SEPTEMBER 1993	Examiner SIATOU E.
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